AMENDMENT

Please amend the above-captioned application as follows:

In the Claims

Please cancel claims 2, 4, 11, 44, 47, 51, 55, 57 and 60 without prejudice.

Please change the claims as follows:

3. (Twice amended) The computer program product of claim 53, wherein said amino acid residues used to define said functional site are selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr and Val.

F1

5. (Twice amended) The computer program product of claim 53, wherein each geometric constraint within said one or more geometric constraints is selected from the group consisting of an atomic position specified by a set of three dimensional coordinates, an interatomic distance, and an interatomic angle.

F2

6. (Three times amended) The computer program product of claim 5, wherein at least one member of said one or more geometric constraints is an atomic position specified by a set of three dimensional coordinates, and said three dimensional coordinates are associated with a preselected root mean square deviation variance.

F3

8. (Twice amended) The computer program product of claim 5, wherein at least one member of said one or more geometric constraints is an interatomic distance.

F4

9. (Twice amended) The computer program product of claim 5, wherein at least one member of said one or more geometric constraints is an interatomic angle.

10. (Twice amended) The computer program product of claim 53, wherein said functional site descriptor further comprises a conformational constraint.

12. (Twice amended) The computer program product of claim 53, wherein all of the atoms for which geometric constraints are provided are selected from the group consisting of protein backbone α-carbons, amide nitrogens, carbonyl carbons and carbonyl oxygens.

13. (Twice amended) The computer program product of claim 53, wherein at least one of said one or more atoms in said amino acids used to define said functional site is a pseudoatom.

14. (Twice amended) The computer program product of claim 13, wherein the pseudoatom is a center of mass with respect to at least two atoms selected from at least two amino acid residues used to define said functional site.

16. (Twice amended) The computer program product of claim 53, wherein the functional site descriptor defines a functional site of a protein corresponding to a function selected from the group consisting of disulfide oxidoreductase activity, α/β hydrolase activity, phospholipase activity, and T1 ribonuclease activity.

18. (Twice amended) The computer program product of claim 53, wherein the functional site descriptor defines a function selected from the group consisting of an enzyme active site, a ligand binding domain, and a protein-protein interaction domain.

F7 cont

19. (Twice amended) The computer program product of claim 18, wherein said ligand binding domain binds a ligand selected from the group consisting of a substrate, a co-factor, and an antigen.

F8

22. (Twice amended) The computer program product of claim 20, wherein the library comprises at least two functional site descriptors for one or more functions of a protein or family of proteins.

F9

45. (Three times amended) A computer program product comprising a computer readable medium having executable instructions representing a computer program recorded thereon, said executable instructions comprising a computer program for creating a functional site descriptor, wherein the functional site descriptor identifies a functional site using at least one atom from each of about fifteen or fewer amino acid residues used to define said functional site, said functional site corresponding to a function of a protein or family of proteins, said computer program comprising:

(a) program code for determining an amino acid residue identity constraint for each amino acid residue used to define said functional site, wherein said amino acid residue identity constraint for each amino acid residue is a single amino acid residue identity or two or more alternative amino acid residue identities;

(b) program code for determining one or more geometric constraints between at least three different atoms, wherein at least three of said different atoms are in different amino acid residues of the protein used to define said functional site and at least one of said atoms is selected from the group consisting of a backbone amide nitrogen, an alpha-

carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen; and,

F9 cont'd

(c) program code for assigning a variance to each geometric constraint in order to provide a degree of relaxation for each said geometric constraint; and,

(d) program code for causing a computer to output said constraints comprising functional site descriptor created for said functional site to a storage device or a display device.

48. (Twice amended) The computer program product of claim 45, wherein said set of geometric constraints further comprises one or more geometric constraints with respect to one or more atoms or pseudoatoms of one or more amino acid residues that are adjacent to an amino acid residue used to define said functional site.

F10

49. (Twice amended) The computer program product of claim 45, wherein said set of geometric constraints comprises geometric constraints selected from the group consisting of an atomic position specified by a set of three dimensional coordinates, an interatomic distance, and an interatomic angle.

50. (Twice amended) The computer program product of claim 45, wherein at least one of the geometric constraints of said set of geometric constraints comprises an interatomic distance between atoms and/or pseudoatoms.

52. (Twice amended) The computer program product of claim 68 or 69, wherein said operation of modifying one or more geometric constraints of said set of geometric constraints to produce a modified set of geometric constraints comprises:

computing an average value for a geometric constraint within the set of geometric constraints by determining values for said geometric constraint from at least two different proteins having functional sites that correlate with said biological function, and calculating said average value;

computing a standard deviation with respect to such geometric constraint; and

applying a multiplier to said computed standard deviation to generate said modified geometric constraint.

53. (Twice amended) A computer program product comprising a computer readable medium having executable instructions representing a computer program recorded thereon, said executable instructions comprising a functional site descriptor, wherein the functional site descriptor defines a functional site corresponding to a function of a protein or family of proteins, other than a divalent metal ion binding site, the functional site descriptor being defined using at least one atom from each of about fifteen or fewer amino acid residues used to define said functional site and comprising:

(a) an amino acid residue identity constraint for each amino acid residue used to define said functional site, wherein said amino acid residue identity constraint for each amino acid residue is a single amino acid residue identity or two or more alternative amino acid residue identities;

(b) one or more geometric constraints for at least three different atoms, wherein at least three of said different atoms are in different amino acid residues of the protein used to define said functional site and at least one of said atoms is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen; and,

(c) each geometric constraint is associated with a variance in order to provide a degree of relaxation for each said geometric constraint.

54. (Twice amended) A computer implemented method for determining a functional site descriptor, wherein the functional site descriptor defines a functional site corresponding to a function of a protein or family of proteins other than a divalent metal ion binding site, the functional site descriptor being defined using at least one atom from each of about fifteen or fewer amino acid residues used to define said functional site, comprising the following steps:

(a) identifying an amino acid residue identity constraint for each amino acid residue used to define said functional site, wherein said amino acid residue identity constraint for each amino acid residue is a single amino acid residue identity or two or more alternative amino acid residue identities;

(b) identifying one or more geometric constraints for at least three different atoms, wherein at least three of said different atoms are in different amino acid residues of the protein used to define said functional site and at least one of said atoms is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a

backbone carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen; and,

(c) providing a variance for association with each geometric constraint in order to provide a degree of relaxation for each said geometric constraint.

56. (Twice amended) A computer-implemented method for defining a functional site descriptor, wherein the functional site descriptor defines a functional site corresponding to a function of a protein or family of proteins, the functional site descriptor being defined using at least one atom from each of about fifteen or fewer amino acid residues used to define said functional site, comprising the following steps:

(a) identifying an amino acid residue identity constraint for each amino acid residue used to define said functional site, wherein said amino acid residue identity constraint for each amino acid residue is a single amino acid residue identity or two or more alternative amino acid residue identities;

(b) identifying one or more geometric constraints for at least three different atoms, wherein at least three of said different atoms are in different amino acid residues of the protein used to define said functional site and at least one of said atoms is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen; and,

(c) providing a variance for association with each geometric constraint in order to provide a degree of relaxation for each said geometric constraint.

58. (Amended) A computer system, comprising:

(a) a processor; and

(b) a computer program product as set forth in claim 45.

59. (Amended) A computer system, comprising:

(a) a processor; and

(b) a computer program product as set forth in claim 53.

Please add the following new claims 61 to 116:

--61. The computer program product of claim 53, wherein the functional site descriptor defines a functional site of a protein corresponding to a function selected from the group consisting of protein kinase activity, phosphorylase kinase activity, protein-tyrosine kinase activity, serine/threonine specific protein phosphatase activity, protein-tyrosine-phosphatase activity, chymotrypsin activity, trypsin activity, and thrombin activity.

62. The computer program product of claim 17, wherein the functional site descriptor is a three atom functional site descriptor.

63. The computer program product of claim 17, wherein the functional site descriptor is a six atom functional site descriptor.

64. The computer program product of claim 17, wherein the functional site descriptor is a nine atom functional site descriptor.

65. The computer program product of claim 17, wherein the functional site descriptor is a twelve atom functional site descriptor.

66. The computer program product of claim 45 wherein at least two of said three different atoms are selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen.

67. The computer program product of claim 45 wherein three of said three different atoms are selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen.

F15 cont

68. The computer program product of claim 45, which further comprises:

(e) program code for modifying one or more geometric constraints of said set of geometric constraints to produce a modified set of geometric constraints for said functional site;

(f) program code for comparing said modified set of geometric constraints to a data set of functional sites correlated with said biological function to determine whether said modified set of geometric constraints compares favorably with said data set of functional sites correlated with said biological function and, optionally, program code for comparing said modified set of geometric constraint(s) to a data set of functional sites not correlated with said

biological function to determine whether said modified set of geometric constraints compares favorably with said data set of functional sites not correlated with said biological function; and,

(g) program code for selecting a set geometric constraints that is preferred for distinguishing between proteins known to contain said functional site and proteins known not to contain said functional site; and,

(h) program code for causing a computer to output said preferred set of geometric constraints for said functional site to a storage device or a display device.

69. The computer program product of claim 68 which further comprises program code for repeating said modifying and comparing operations of steps (e) and (f) to modify one or more of said geometric constraints of said set of geometric constraints to identify a modified set of geometric constraints that compares favorably with said data set of functional sites correlated with said biological function without encompassing a predetermined amount of data sets not correlated with said biological function.

FIS cont

70. The computer program product of claim 45, wherein the functional site descriptor defines a functional site of a protein corresponding to a function selected from the group consisting of disulfide oxidoreductase activity, α/β hydrolase activity, phospholipase activity, and T1 ribonuclease activity.

71. The computer program product of claim 45, wherein the functional site descriptor is selected from the group consisting of a three atom functional site descriptor, a four atom functional site descriptor, a five atom functional site descriptor, a six atom functional site descriptor, a seven atom functional site descriptor, an eight atom functional site descriptor, a nine

atom functional site descriptor, a ten atom functional site descriptor, an eleven atom functional site descriptor, a twelve atom functional site descriptor, a thirteen atom functional site descriptor, a fourteen atom functional site descriptor, and a fifteen atom functional site descriptor.

72. The computer program product of claim 45, wherein the functional site descriptor defines a functional site of a protein corresponding to a function selected from the group consisting of protein kinase activity, phosphorylase kinase activity, protein-tyrosine kinase activity, serine/threonine specific protein phosphatase activity, protein-tyrosine-phosphatase activity, chymotrypsin activity, trypsin activity, and thrombin activity.

FIS
CONT

73. The computer program product of claim 45, wherein the functional site descriptor defines a function selected from the group consisting of an enzyme active site, a ligand binding domain, and a protein-protein interaction domain.

74. The computer program product of claim 45, wherein said ligand binding domain binds a ligand selected from the group consisting of a substrate, a co-factor, and an antigen.

75. The method of claim 54, wherein said amino acid residues used to define said functional site are selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr and Val.

76. The method of claim 54, wherein each geometric constraint within said one or more geometric constraints is selected from the group consisting of an atomic position

specified by a set of three dimensional coordinates, an interatomic distance, and an interatomic angle.

77. The method of claim 54, wherein at least one member of said one or more geometric constraints is an atomic position specified by a set of three dimensional coordinates, and said three dimensional coordinates are associated with a preselected root mean square deviation variance.

78. The method of claim 77, wherein the atomic position varies within a root mean square deviation of less than about 3 Å.

F15 cont

79. The method of claim 76, wherein at least one member of said one or more geometric constraints is an interatomic distance.

80. The method of claim 76, wherein at least one member of said one or more geometric constraints is an interatomic angle.

81. The method of claim 54, wherein said functional site descriptor further comprises a conformational constraint.

82. The method of claim 54, wherein all of the atoms for which geometric constraints are provided are selected from the group consisting of protein backbone α-carbons, amide nitrogens, carbonyl carbons and carbonyl oxygens.

83. The method of claim 54, wherein at least one of said one or more atoms in said amino acids used to define said functional site is a pseudoatom.

84. The method of claim 83, wherein the pseudoatom is a center of mass with respect to at least two atoms selected from at least two amino acid residues used to define said functional site.

85. The method of claim 54, wherein the functional site descriptor defines a functional site of a protein corresponding to a function selected from the group consisting of disulfide oxidoreductase activity, α/β hydrolase activity, phospholipase activity, and T1 ribonuclease activity.

F15 CONT

86. The method of claim 54, wherein the functional site descriptor is selected from the group consisting of a three atom functional site descriptor, a four atom functional site descriptor, a five atom functional site descriptor, a six atom functional site descriptor, a seven atom functional site descriptor, an eight atom functional site descriptor, a nine atom functional site descriptor, a ten atom functional site descriptor, an eleven atom functional site descriptor, a twelve atom functional site descriptor, a thirteen atom functional site descriptor, a fourteen atom functional site descriptor, and a fifteen atom functional site descriptor.

87. The method of claim 54, wherein the functional site descriptor defines a functional site of a protein corresponding to a function selected from the group consisting of protein kinase activity, phosphorylase kinase activity, protein-tyrosine kinase activity, serine/threonine specific protein phosphatase activity, protein-tyrosine-phosphatase activity, chymotrypsin activity, trypsin activity, and thrombin activity.

88. The method of claim 54, wherein the functional site descriptor defines a function selected from the group consisting of an enzyme active site, a ligand binding domain, and a protein-protein interaction domain.

89. The method of claim 88, wherein said ligand binding domain binds a ligand selected from the group consisting of a substrate, a co-factor, and an antigen.

90. The method of claim 54 which further comprises repeating said in order to determine a library of functional site descriptors.

F15 Cont

91. The method of claim 90, wherein the library comprises at least two functional site descriptors for one or more functions of a protein or family of proteins.

92. A method for creating a functional site descriptor, said functional site corresponding to a function of a protein or family of proteins and said functional site descriptor identifying a functional site using at least one atom from each of about fifteen or fewer amino acid residues used to define said functional site, comprising the steps of:

(a) determining an amino acid residue identity constraint for each amino acid residue used to define said functional site, wherein said amino acid residue identity constraint for each amino acid residue is a single amino acid residue identity or two or more alternative amino acid residue identities;

(b) determining one or more geometric constraints between at least three different atoms, wherein at least three of said different atoms are in different amino acid residues of the protein used to define said functional site and at least one of said atoms is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone

carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen; and,

(c) assigning a variance to each geometric constraint in order to provide a degree of relaxation for each said geometric constraint.

93. The method of claim 92, wherein said functional site descriptor further comprises a conformational constraint.

94. The method of claim 92, wherein all of the atoms for which geometric constraints are provided are selected from the group consisting of protein backbone α-carbons, amide nitrogens, carbonyl carbons and carbonyl oxygens.

F15 cont

95. The method of claim 92, wherein at least one of said one or more atoms in said amino acids used to define said functional site is a pseudoatom.

96. The method of claim 95, wherein the pseudoatom is a center of mass with respect to at least two atoms selected from at least two amino acid residues used to define said functional site.

97. The method of claim 92, wherein the functional site descriptor defines a functional site of a protein corresponding to a function selected from the group consisting of disulfide oxidoreductase activity, α/β hydrolase activity, phospholipase activity, and T1 ribonuclease activity.

98. The method of claim 92, wherein the functional site descriptor is selected from the group consisting of a three atom functional site descriptor, a four atom functional site descriptor, a five atom functional site descriptor, a six atom functional site descriptor, a seven atom functional site descriptor, an eight atom functional site descriptor, a nine atom functional site descriptor, a ten atom functional site descriptor, an eleven atom functional site descriptor, a twelve atom functional site descriptor, a thirteen atom functional site descriptor, a fourteen atom functional site descriptor, and a fifteen atom functional site descriptor.

99. The method of claim 92, wherein the functional site descriptor defines a functional site of a protein corresponding to a function selected from the group consisting of protein kinase activity, phosphorylase kinase activity, protein-tyrosine kinase activity, serine/threonine specific protein phosphatase activity, protein-tyrosine-phosphatase activity, chymotrypsin activity, trypsin activity, and thrombin activity.

FIS cont

100. The method of claim 92, wherein the functional site descriptor defines a function selected from the group consisting of an enzyme active site, a ligand binding domain, and a protein-protein interaction domain.

101. The method of claim 100, wherein said ligand binding domain binds a ligand selected from the group consisting of a substrate, a co-factor, and an antigen.

102. The method of claim 92 which further comprises repeating said in order to determine a library of functional site descriptors.

103. The method of claim 102, wherein the library comprises at least two functional site descriptors for one or more functions of a protein or family of proteins.

104. A computer system for determining the existence of a functional site in a test protein comprising:

(a) means for applying a functional site descriptor to a test protein; and,

(b) means for creating and displaying an output representing the assignment or non-assignment of the function assigned to said functional site descriptor to said test protein.

F15 cont

105. A machine having a memory that contains data representing a functional site descriptor generated by the method of any of claims 54, 56, or 92.

106. A method for creating a functional site descriptor corresponding to the active site of a protein or family of proteins, comprising the steps of:

(a) determining an amino acid residue identity constraint for each of three amino acid residues used to define said active site, wherein said amino acid residue identity constraint for each amino acid residue is a single amino acid residue;

(b) determining one or more geometric constraints between at least nine atoms, wherein each atom is located in a different amino acid, and wherein said different amino acids comprise the three amino acid residues used to define said active site and the two amino acids residues immediately adjacent to each of said three amino acids, at least one of said atoms being selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, and a

pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen; and,

(c) assigning a variance to each geometric constraint in order to provide a degree of relaxation for each said geometric constraint.

107. The method of claim 106 wherein said geometric constraint is distance.

108. The method of claim 107 wherein the geometric constraint comprises nine distances between the α-carbons of the three amino acids used to define said active site and the α-carbons of the amino acids adjacent to each of said three amino acids.

F-15 cont

109. The computer program product of claim 53 wherein said functional site is a protein active site, said amino acid residue identity constraint comprises three amino acids used to define said protein active site, and said one or more geometric constraints comprises nine distances between the α-carbons of said three amino acids and the α-carbons of the amino acids adjacent to each of said three amino acids.

110. The computer program product of claim 45 wherein said functional site is a protein active site, said amino acid residue identity constraint comprises three amino acids used to define said protein active site, and said one or more geometric constraints comprises nine distances between the α-carbons of said three amino acids and the α-carbons of the amino acids adjacent to each of said three amino acids.

111. The method of claim 54 wherein said functional site is a protein active site, said amino acid residue identity constraint comprises three amino acids used to define said

protein active site, and said one or more geometric constraints comprises nine distances between the α-carbons of said three amino acids and the α-carbons of the amino acids adjacent to each of said three amino acids.

112. The method of claim 56 wherein said functional site is a protein active site, said amino acid residue identity constraint comprises three amino acids used to define said protein active site, and said one or more geometric constraints comprises nine distances between the α-carbons of said three amino acids and the α-carbons of the amino acids adjacent to each of said three amino acids.

FIS cont

113. The method of claim 91 wherein said functional site is a protein active site, said amino acid residue identity constraint comprises three amino acids used to define said protein active site, and said one or more geometric constraints comprises nine distances between the α-carbons of said three amino acids and the α-carbons of the amino acids adjacent to each of said three amino acids.

114. The computer system of claim 103 wherein said functional site descriptor defines a protein active site, the amino acid residue identity constraint of said functional site descriptor comprises three amino acids used to define said protein active site, and the geometric constraints of said functional site descriptor comprise nine distances between the α-carbons of said three amino acids and the α-carbons of the amino acids adjacent to each of said three amino acids.

115. The machine of claim 104 wherein said functional site descriptor defines a protein active site, the amino acid residue identity constraint of said functional site descriptor

comprises three amino acids used to define said protein active site, and the geometric constraints of said functional site descriptor comprise nine distances between the α-carbons of said three amino acids and the α-carbons of the amino acids adjacent to each of said three amino acids.

116. A computer program product comprising a computer readable medium having executable instructions representing a computer program recorded thereon, said executable instructions comprising a functional site descriptor, wherein the functional site descriptor defines a functional site corresponding to a function of a protein or family of proteins, other than a divalent metal ion binding site, and the functional site descriptor is a three-dimensional representation of a protein functional site, and comprising:

F15 cont

(a) an amino acid residue identity constraint for each amino acid residue used to define said functional site, wherein said amino acid residue identity constraint for each amino acid residue is a single amino acid residue identity or two or more alternative amino acid residue identities;

(b) one or more geometric constraints for at least three different atoms, wherein at least three of said different atoms are in different amino acid residues of the protein used to define said functional site and at least one of said atoms is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen; and,

(c) each geometric constraint is associated with a variance in order to provide a degree of relaxation for each said geometric constraint.--